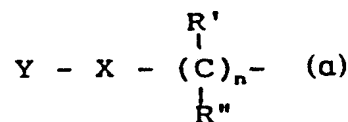
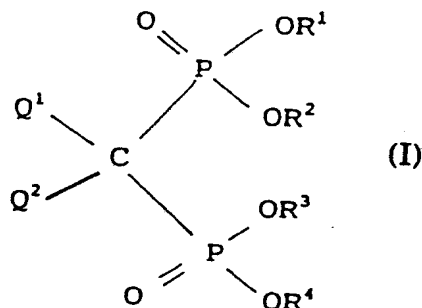




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**(54) Title:** NOVEL METHYLENEBISPHOSPHONIC ACID DERIVATIVES



**(57) Abstract**

Novel pharmacologically active methylenebisphosphonates having formula (I) wherein R<sup>1</sup>-R<sup>4</sup> independently are C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>3</sub>-C<sub>10</sub>-cycloalkyl, aryl, aralkyl, silyl SiR<sub>3</sub> or hydrogen, whereby in formula (I) at least one of the groups R<sup>1</sup>-R<sup>4</sup> is hydrogen and at least one of the groups R<sup>1</sup>-R<sup>4</sup> is different from hydrogen, Q<sup>1</sup> is hydrogen, hydroxyl, halogen, amino NH<sub>2</sub>, or OR<sup>1</sup>, wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub>-alkyl or acyl, Q<sup>2</sup> is the group (α) wherein Y is a six-membered heterocyclic group, or a carbocyclic aromatic group, X is a bond, O, S or NR<sup>'''</sup>, wherein R<sup>'''</sup> is hydrogen, lower alkyl, or acyl, n is the integer 0 to 6, and R' and R'' are hydrogen or lower alkyl provided that as a ring atom of the ring Y and/or a chain atom of the group X, there is always at least one heteroatom from the group of O, N and S, including the stereoisomers and the salts of the compounds.

**+ DESIGNATIONS OF "SU"**

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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# Novel methylenebisphosphonic acid derivatives

The invention concerns novel methylenebisphosphonic acid derivatives substituted at the methylene carbon, in particular novel bisphosphonic ester acids and ester salts substituted at the methylene carbon, as well as processes for the preparation of these novel compounds, and pharmaceutical formulations comprising these novel compounds.

Several publications disclose methylenebisphosphonic acids, their salts or some tetraesters, but there are only a few disclosures of corresponding partial esters, tri-, di- and monoesters.

In the patents US 4,447,256 and DE 28 31 578 (Suzuki et al.) a process is disclosed for the preparation of some pyridyl aminomethylenebisphosphonic acid tetraethyl esters. According to the patents the compounds may be used as herbicides, however, no disclosure is found of a pharmaceutical effect of the compounds.

In the patent EP 337 706 (Isomura et al.) the preparation of such cyclyl- or heterocyclyl substituted aminomethylenebisphosphonic acid tetraesters is disclosed, wherein the ring substituent is either partly or fully saturated.

In the patent EP 282 320 (Sakamoto et al.) the preparation of some isoxazolyl substituted aminomethylenebisphosphonic acid tetraalkyl esters as well as the preparation of two partial esters is disclosed.

In the patent EP 298 553 (F.H. Ebetino) the preparation of methylenephosphonoalkyl phosphinates, substituted at the methylene carbon, is disclosed.

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The preparation of tetraesters of methylenebisphosphonic acids has been described also in the publications: J. Am.

Chem. Soc. 78, (1956) 4450; J. Chem. Soc. (1959) 2272; J. Am. Chem. Soc. 84 (1962) 1876; J. Org. Chem. 35, (1970) 3149; J. Org. Chem. 36, (1971) 3843 and Phosphorus, Sulfur and Silicon 42, (1989) 73, EP patent application 221 611.

5

According to the invention it has been discovered that the novel substituted partial esters of methylenebisphosphonic acids and their salts in many cases exhibit more favourable properties than the corresponding bisphosphonic acids and salts due to their better kinetics and availability, their ability to participate as complex formers in the regulation of the metabolism of the organism being maintained.

10

They are well suited for the treatment of disorders relating to the metabolism of calcium and of other, especially bivalent metals. They may be used both for the treatment of diseases in the skeletal system, especially of bone formation and resorption disorders, such as of osteoporosis and Paget's disease, as well as for the treatment of diseases in the soft tissues, such as of deposition and mineralisation conditions and bone formation disorders.

15

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On the other hand, being pyrophosphate analogs, the new substituted methylenebisphosphonic acid derivatives also are suitable for the treatment of disorders in the (pyro)phosphate functions of the organism, including those functions, wherein an active, but disturbance-prone or wrongly functioning organic part is coupled to (pyro)phosphate or acts as a metal complex or a combination of the last mentioned.

25

30

The novel bisphosphonates regulate either directly or over an indirect mechanism the quality and level of cations and/or pyrophosphate compounds freely present in the body fluids as well as of that binding to, active in and liberated from the tissues. Thus they are able to regulate the cellular metabolism, growth and destruction. Consequently

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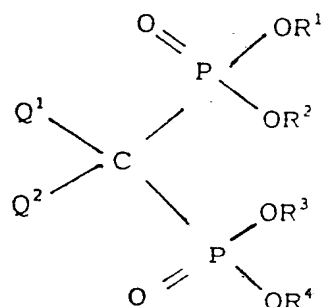
they are useful for the treatment of e.g. cancer of the bone and metastases thereof, ectopic calcifications, urolithiasis, rheumatoid arthritis, bone infections and bone degradation.

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Typical for the novel substituted methylenebisphosphonates is a selective desired and controlled action, providing for a better therapeutic index.

10 The invention concerns novel methylenebisphosphonic acid derivatives of the general formula I

15



I

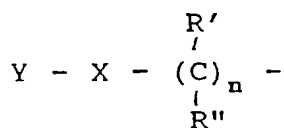
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in which formula

$R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  independently are a straight or branched, optionally unsaturated  $C_1$ - $C_{10}$ -alkyl, optionally unsaturated  $C_3$ - $C_{10}$ -cycloalkyl, aryl, aralkyl, silyl  $\text{SiR}_3$  or hydrogen, whereby in the formula I at least one of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  is hydrogen and at least one of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  is different from hydrogen,

30  $Q^1$  is hydrogen, hydroxyl, halogen, amino  $\text{NH}_2$ , or  $\text{OR}'_1$ , wherein  $R'_1$  is  $C_1$ - $C_4$ -alkyl or acyl,

$Q^2$  is the group



35

wherein Y is an optionally substituted, saturated, partly saturated or aromatic six-membered heterocyclic group, or a carbocyclic aromatic group, whereby the heterocyclic groups can contain 1 to 3 heteroatoms from the group N, O and S, X is a bond, O, S or NR'', wherein R'' is hydrogen or lower alkyl with 1 to 4 C-atoms, acyl, n is the integer 0 to 6, and R' and R'' are independently hydrogen or lower alkyl with 1 to 4 C-atoms, provided that as a ring atom of the ring Y and/or a chain atom of the group X, there is always at least one heteroatom from the group of O, N and S, including the stereoisomers, such as the geometrical isomers and the optically active isomers, of the compounds, as well as the pharmacologically acceptable salts of the compounds.

The groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently a straight or branched alkyl, alkenyl or alkynyl group and they contain 1 to 10, respectively 2 to 10 carbon atoms, preferably 1 to 7, respectively 2 to 7, and advantageously 1 to 4, respectively 2 to 4 carbon atoms.

Optionally unsaturated cycloalkyl is cycloalkyl or cycloalkenyl with 3 to 10 C-atoms, preferably, however, cyclopropyl, -butyl, -pentyl, or -hexyl.

Aryl or aralkyl as the groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> means optionally C<sub>1</sub>-C<sub>4</sub>-lower alkyl, -lower alkoxy or halogen substituted monocyclic aryl or aralkyl, such as phenyl and benzyl, preferably, however, unsubstituted phenyl or benzyl.

Halogen is fluorine, chlorine, bromine or iodine.

Acyl is alkyl-, aryl- or arylalkylcarbonyl, or alkoxy-, aryloxy- or aralkoxycarbonyl, wherein alkyl contains 1 to

4 carbon atoms, and aryl and aralkyl have the same meaning as before.

In the silyl group  $\text{SiR}_3$ , the group R is lower alkyl containing 1 to 4 C-atoms, and is especially methyl, ethyl, isopropyl, butyl, t-butyl, or it is phenyl or R-substituted phenyl, whereby also different combinations of lower alkyl and phenyl groups come into question, such as dimethyl t-butyl, methyl diisopropyl, dimethyl phenyl, diethyl phenyl, methyl t-butyl phenyl, diisopropyl-(2,6-dimethyl phenyl).

As the heteroaromatic and saturated heterocyclic group Y, respectively, nitrogen, oxygen and/or sulfur containing six-membered unsaturated ring groups come into question, such as pyridine, pyrimidine, pyrazine, pyridazine, oxazine, thiazine, triazine, as well as corresponding saturated groups, such as piperidine, piperazine, morpholine, oxathiane, dithiane, thiomorpholine etc. The heterocyclic groups may be substituted as has been described for aryl and aralkyl below.

The group Y means as a carbocyclic aromatic group a substituted or unsubstituted aromatic ring, such as a monocyclic aryl or aralkyl, especially phenyl, or a conjugated or bridged unsaturated or partly saturated ring system, such as naphthyl, phenanthryl, indenyl, indanyl, tetrahydronaphthyl, biphenyl, di- and triphenyl methyl etc.

Monocyclic aryl and aralkyl may be illustrated with the formula



wherein the groups  $D'$  mean independently  $C_1$ - $C_4$ -alkyl, -alkoxy, halogen or nitro,  $m'$  is the integer 0 to 3 and  $m$  the integer 0 or 1, and  $D$  means a straight or branched  $C_1$ -

C<sub>6</sub>-alkylene, -alkenylene or -alkynylene. Halogen is chlorine, bromine, fluorine or iodine.

5 The group Y-X- in the formula I contains at least one heteroatom from the group O, N and S as a ring atom in Y and/or as chain atom in X.

Salts of the compounds of the formula I are especially their salts with pharmaceutically acceptable bases, such as  
10 metal salts, for example alkalimetal salts, especially lithium, sodium and potassium salts, alkaline earth metal salts, such as calcium or magnesium salts, copper, aluminium or zinc salts, as well as ammonium salts with ammonia or with primary, secondary and tertiary, both aliphatic and  
15 alicyclic as well as aromatic amines, and quaternary ammonium salts, such as halides, sulphates and hydroxides, salts with aminoalcohols, such as ethanol-, diethanol- and triethanolamines, tris(hydroxymethyl)aminomethane, 1- and 2-methyl- and 1,1-, 1,2- and 2,2-dimethylaminoethanols, N-  
20 mono- and N,N-dialkylaminoethanols, N-(hydroxymethyl- and ethyl)-N,N-ethanediamines, as well as amino crown ethers and cryptates, and heterocyclic ammonium salts, such as azetidinium, pyrrolidinium, piperidinium, piperazinium, morpholinium, pyrrolium, imidazolium, pyridinium, pyrimidin-  
25 dinium, quinolinium, etc., salts.

Good results have been obtained with the following mono- or dimethyl-, mono- or diethyl-, mono- or diisopropyl esters, wherein Q<sup>1</sup> is hydrogen and Y is a heterocyclic group, such  
30 as unsubstituted or methyl substituted pyridine or piperidine, n is 0, and X is NH or S, and especially good results have been obtained with the following compounds:

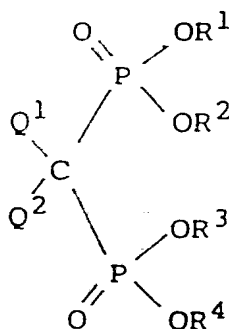
35 [[(6-methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester,  
[[ (2-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester,



- [[ (2-pyridinyl) amino] methylidene] bisphosphonic acid P,P'-methyl ester,  
[[ (3-methyl-2-pyridinyl) amino] methylidene] bisphosphonic acid P,P'-diethyl ester,  
5 [[ (4-methyl-2-pyridinyl) amino] methylidene] bisphosphonic acid P,P'-diethyl ester,  
[[ (2-pyridinyl) thio] methylidene] bisphosphonic acid monoisopropyl ester,  
[[ (4-chlorophenyl) thio] methylidene] bisphosphonic acid  
10 P,P'-dimethyl and monoethyl ester,  
[[ (6-methyl-2-pyridinyl) amino] methylidene] bisphosphonic acid monoethyl ester,  
[[ (3-methyl-2-pyridinyl) amino] methylidene] bisphosphonic acid monomethyl ester,  
15 [[ 1-hydroxy-2-(3-pyridinyl) ] ethylidene] bisphosphonic acid monoisopropyl ester,  
[[ 1-hydroxy-2-(3-pyridinyl) ] ethylidene] bisphosphonic acid monomethyl ester,  
[ 2-(2-pyridinyl) ethylidene] bisphosphonic acid monoisopropyl  
20 ester,  
[ 2-(3-pyridinyl) ethylidene] bisphosphonic acid monomethyl ester,  
[[ (3-pyridinyl) amino] methylidene] bisphosphonic acid P,P'-dimethyl ester,  
25 [[ (3-pyridinyl) thio] methylidene] bisphosphonic acid P,P'-diethyl ester,  
[[ (4-pyridinyl) thio] methylidene] bisphosphonic acid P,P'-diethyl ester,  
[[ (3-pyridinyl) thio] methylidene] bisphosphonic acid monoisopropyl ester.  
30

The invention concerns also a process for the preparation of the compounds of the formula I, according to which  
a) a methylenebisphosphonic acid tetraester of the formula  
35 II

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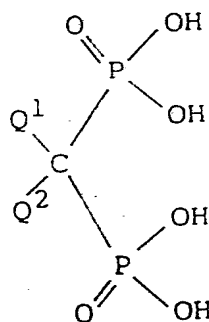
10 in which formula  $\text{Q}^1$  and  $\text{Q}^2$  have the same meaning as above, and  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  have the same meaning as above, except hydrogen, is selectively hydrolysed

- to a triester corresponding to the formula I, wherein one of the groups  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  has the meaning of  
15 hydrogen, or a salt thereof, or

- to a diester corresponding to the formula I, wherein two of the groups  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  have the meaning of hydrogen, or a salt thereof, or

- to a monoester corresponding to the formula I, wherein three of the groups  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  have the meaning of hydrogen, or a salt thereof, or  
20

b) a bisphosphonic acid of the formula



25

VII

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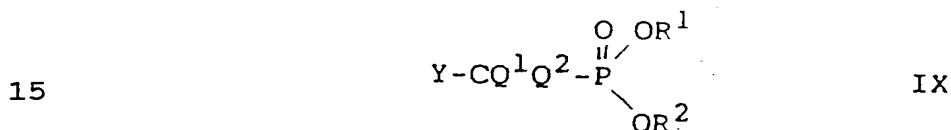
or a metal or ammonium salt of this compound, or the corresponding acid tetrachloride, wherein  $\text{Q}^1$  and  $\text{Q}^2$  have the same meaning as above, is esterified selectively by reacting the same with an esterification reagent corresponding  
35 to the desired groups  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$ ,

- to a monoester corresponding to the formula I, wherein three of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  have the meaning of hydrogen, or

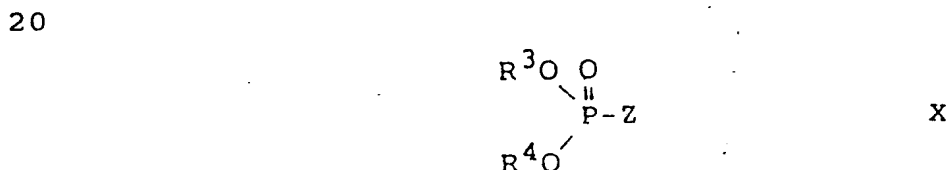
- to a diester corresponding to the formula I, wherein  
5 two of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  have the meaning of hydrogen, or

- to a triester corresponding to the formula I, wherein one of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  has the meaning of hydrogen, or to the corresponding ester salts of the said  
10 partial esters, or

c) a phosphonate having the formula



is reacted with an activated phosphate or a hydrogen phosphonate corresponding to the formula X



25 wherein in the formulas Y is hydrogen, hydroxy or halogen or other leaving group, Z is hydrogen, halogen, acyloxy, sulphonyloxy, alkoxy or aryloxy, and  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  and  $Q^1$  and  $Q^2$  have the same meaning as in the formula I, or  $Q^1$  and  $Q^2$  form a double-bonded oxygen or an imino group, or is  
30 reacted with a phosphite corresponding to the formula X, or

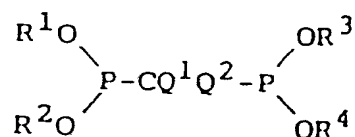
d) a bisphosphonate corresponding to the formula I, which instead of  $Q^2$  has a carbanion site, is reacted with  $\omega$ -leaving group substituted  $Q^2$ , or a bisphosphonate corresponding to the formula I, which instead of  $Q^2$  contains a  
35 leaving group, is reacted with a  $\omega$ -carbanion corres-

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ponding to  $Q^2$ , or a  $(Q^2-C_1)-\omega$ -carbanion is added by Michael addition in alkylidenebisphosphonates, or

e) a bisphosphonite compound having the formula

5



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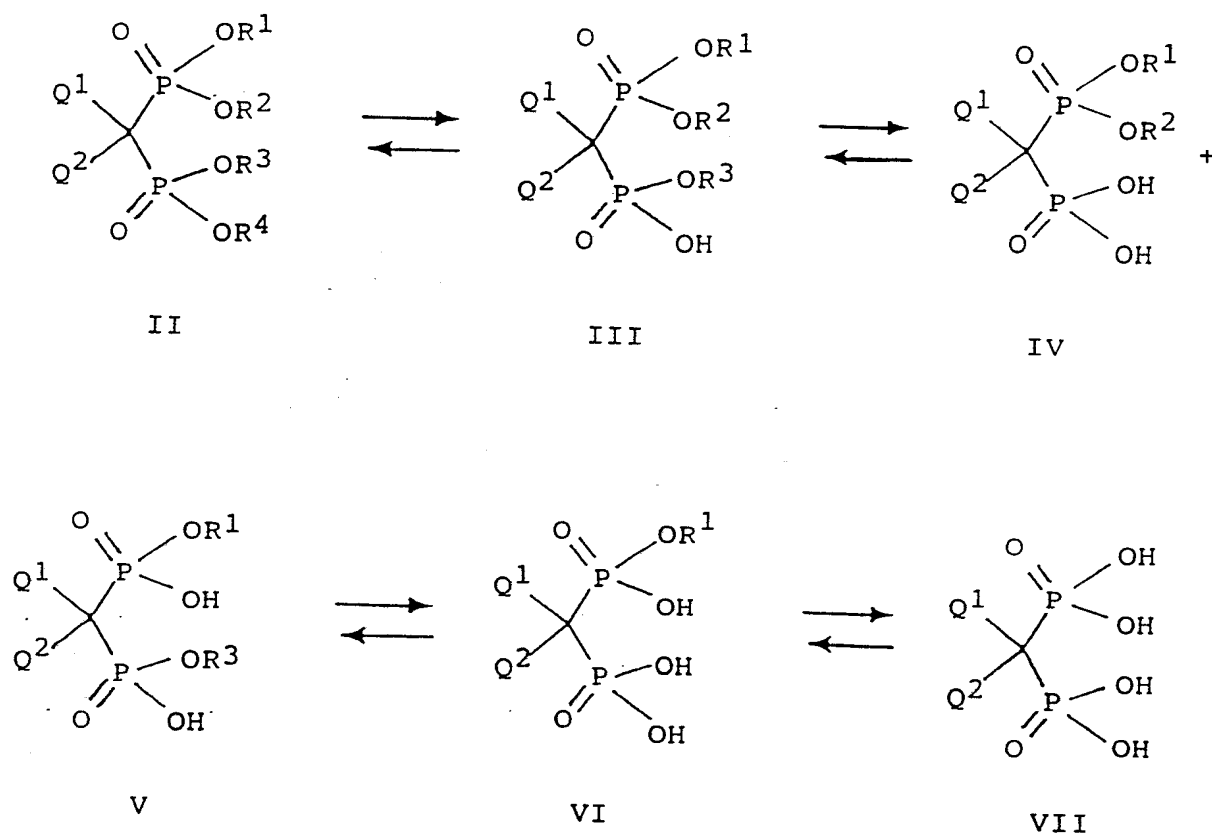
wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  and  $Q^1$  and  $Q^2$  have the same meaning as in the formula I, or the corresponding hydrogen phosphonate compound, is oxidized to a compound of the formula I, and if desired, the partial ester acids obtained according to steps a) to e) are converted to partial ester salts, or the partial ester salts obtained are converted to the partial ester acids, and/or, if desired, a compound obtained according to the formula I is converted into some other compound according to the formula I by hydrolyzing, esterification or transesterification, and/or in a compound of the formula I, a group  $Q^1$  is converted into another group  $Q^1$  within the scope of the definition.

According to one process the compounds are thus prepared by selective hydrolysis of the tetraesters corresponding to the formula I. As the starting material thus a tetraester is used, wherein the groups  $R^1$  to  $R^4$  and  $Q^1$  and  $Q^2$  have the same meaning as above and this tetraester is hydrolyzed stepwise to the triester III, diester IV and V and the monoester VI. If necessary, the partial ester or its salt may be isolated and purified by extraction, fractional crystallization or chromatographically, and if desired, a free acid may be converted into a salt or a salt into the free acid.

35

This reaction is shown in the appended Scheme 1 (the reaction takes place in the direction of the upper arrow).

Scheme 1



The hydrolysis of the tetraesters II may be carried out by treating both with an acid and a base, using thermal cleaving, and in certain cases also using water, alcohols, or other neutral or non-neutral transalkylation, -silylation and -arylation reagents. The hydrolysis takes place advantageously at a temperature range of 10 to 150 °C. The acids are advantageously conventional inorganic acids, such as hydrochloric acid, sulphuric acid, phosphoric acid, and Lewis acids, such as borotrifluoride etherate, titanium tetrachloride, etc., as well as a number of organic acids, such as oxalic acid, formic acid, acetic acid and other carboxylic acids, methanesulphonic acid and other sulphonic acids, such as tosyl acid, further chlorine and fluorine substituted carboxylic and sulphonic acids, such as trichloroacetic acid and trifluoromethanesulphonic acid, and their aqueous solutions.

The bases are advantageously alkali and ammonium hydroxides and ammonia and the aqueous solutions thereof, as well as a number of amines, such as primary, secondary and tertiary amines, such as e.g. diethyl-, triethyl-, diisopropyl- and tributylamine, aniline, N- and N,N-alkyl substituted anilines and heterocyclic amines, such as pyridine, morpholine, piperidine, piperazine etc., and hydrazines, such as N,N-dimethyl hydrazine.

In addition, acids and bases bound to a solid substrate may be used, such as Amberlites, either in the presence of an organic solvent or water or various solvent mixtures, or in the absence thereof.

Further by treating with certain alkalimetals, such as sodium and lithium, or with suitable inorganic salts, such as with sodium iodide, lithium bromide, ammonium chloride and NaBr/PTC, the ester group may be converted to its corresponding salt, such as to the sodium, ammonium and lithium salt.

Thermal cleaving usually takes place at a temperature of about 100 to 400 °C, usually, however, at a temperature of not more than 250 °C. The presence of a suitable catalyst, such as an acid or an acid solution, or a quaternary ammonium salt, makes it possible to perform the reaction faster and at a lower temperature. Certain active substituents, such as benzyl and allyl, may be removed by catalytic reduction or electrolytically.

10

To improve solubility and to control the reaction temperature during the reactions, organic, inert solvents, such as hydrocarbons, lower alcohols and stable ketones and esters, alkyl halides, such as chloroform, dichloromethane and ethane, ethers, such as dioxan, dimethoxy ethane, diglyme, acetonitrile, etc., may be used as co-solvents.

15

When the groups  $R^1$  to  $R^4$  in the tetraester according to the formula II are the same, the hydrolysis takes place stepwise, and it is interrupted when the concentration of the desired partial ester is at its greatest.

20

In order to prepare a specific partial ester structure, it is advantageous to use a tetraester of the formula II wherein the ester groups are not the same, but groups which are different with respect to the hydrolysis rate. It has, for example, been discovered that the hydrolysis rate of alkyl and silyl esters is dependant on the structure as follows:

25

silyl > tert > sec > prim

It is possible to affect the hydrolysis rate by changing also the size and shape of the alkyl and silyl substituent as well as by electronical factors. It is often possible to perform a transesterification in order to change the stepwise hydrolysis of the different ester sites. Especially

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the methyl ester may advantageously be converted to the corresponding acid over a silyl ester.

Pure partial esters may thus be prepared in an advantageous manner by performing a selective hydrolysis of mixed  
5 esters of the formula I, which have been prepared using ester groups which are advantageous from the point of view of hydrolysis.

10 Also other selective hydrolysis reactions known especially from phosphate and monophosphonate chemistry may be used.

The progress of the hydrolysis may be followed for example chromatographically or by means of  $^{31}\text{P}$ -NMR spectroscopy. The  
15 reaction may be interrupted when the level of the desired partial ester is at its greatest and the product may be isolated from the reaction mixture either as the free acid or as a salt by precipitation, extraction or chromatographically, and the salt form may be converted to the free  
20 acid or the free acid to its salt.

The compounds according to this invention may be prepared also by selective esterification of bisphosphonic acids in accordance with the above mentioned reaction Scheme 1 (the  
25 reaction takes place in the direction of the lower arrow).

As a starting material a tetraacid according to the formula VII ( $\text{R}^1$  to  $\text{R}^4 = \text{H}$ ) may then be used, which can be as a free acid or in the form of a salt, such as a metal or ammonium  
30 salt, or the corresponding phosphonic acid tetrachloride may be used, and depending on the desired end result, 1 to 4 equivalents of the desired aliphatic or aromatic alcohol, or the corresponding activated alkylation, silylation and arylation reagents, such as ortoesters, ketene acetals and  
35 other suitable transfer reagents for alkyl, silyl and aryl groups, such as diazo compounds, active carboxylic acid esters, sulphates, etc. The reaction is usually performed



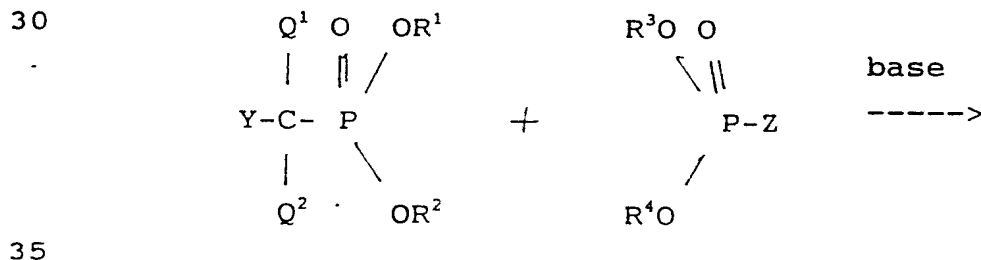
under anhydrous conditions, preferably in the temperature range of 0 to 150°C, or when using an inert co-solvent, at the boiling point thereof.

- 5 The esters II to IV may also be prepared in a nucleophilic substitution reaction between the bisphosphonate anion, often the ammonium salt, and an organic halide or sulphonate, or in a condensation reaction between a phosphonic acid group and a suitable alcohol or a phenol using a reagent  
10 for cleaving off water, such as carbodiimides.

Pure partial esters, also mixed esters, may thus be prepared by selective esterification, if necessary stepwise, of tetraacids of the formula VII. Also other selective  
15 esterification reactions may be applied known primarily from phosphate and monophosphonate chemistry.

The progress of the esterification reactions may be followed, for example, chromatographically or using  $^{31}\text{P}$ -NMR and  
20 the reaction is interrupted when the content of the desired partial ester is at its greatest and this is isolated from the reaction mixture by precipitation, extraction or chromatographically and, if desired, a salt form obtained is converted to the free acid or the free acid is converted to  
25 its salt.

Partial esters according to the invention may also be prepared by constructing the P-C-P frame from its parts



wherein in the formula Y is hydrogen, hydroxy or halogen or other leaving group, Z is halogen, acyloxy, sulphonyloxy,

alkoxy, or aryloxy, and  $R^1$  to  $R^4$  and  $Q^1$  and  $Q^2$  have the meaning given above, or  $Q^1$  and  $Q^2$  are double-bonded oxygen or an imino group. As the base, for example, sodium hydride, butyl lithium or lithium diisopropylamide may be used. In the  
5 starting material optionally present free acid sites (one of the groups  $R^1$  to  $R^4 = H$ ) have to be neutralized, by using a sufficient amount of base, prior to the coupling reaction. Also active sites in the groups  $Q^1$  and  $Q^2$  have to be neutralized or the said active site has to be protected  
10 with a protecting group.

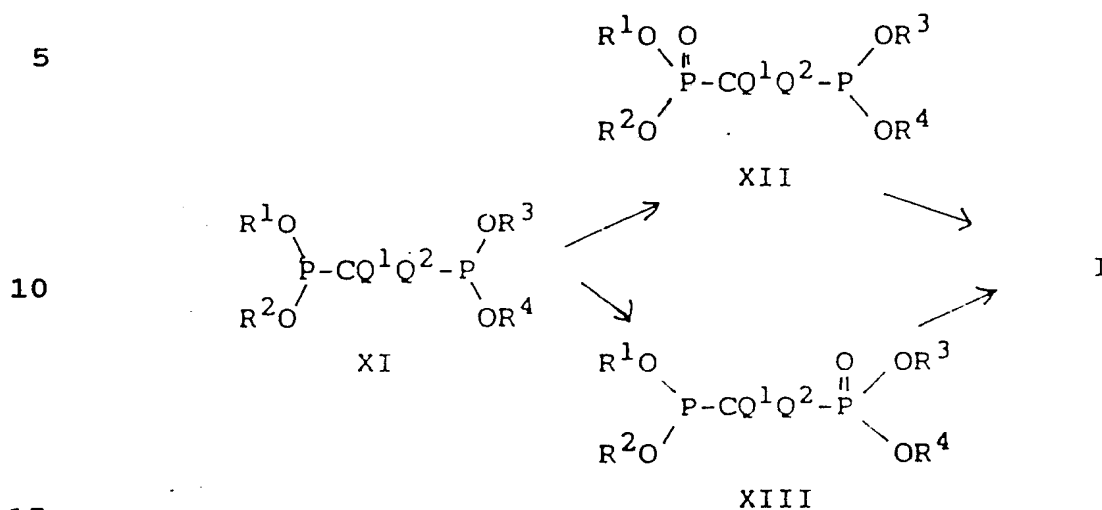
Also the Michaelis-Arbuzov reaction may be used, whereby the second reacting compound is a phosphite, or the Michaelis-Becker reaction, whereby Z is hydrogen.

15 In certain instances the group  $Q^1$  may be introduced by an exchange reaction, or an oxidation or reduction reaction, for example hydroxyl may be obtained from hydrogen, halogen or amino, the amino group may be obtained from halogen or  
20 hydroxyl, and hydrogen may be obtained from halogen, and halogen may be obtained from hydrogen.

$Q^2$  may also be brought into the molecule either by a reaction involving a bisphosphonate carbanion or corresponding C-halogen or other leaving group, whereby the  $Q^2$ -  
25 reagent is  $\omega$ -substituted with a leaving group, or correspondingly is a  $\omega$ -carbanion.

The compounds according to the invention may also be  
30 prepared by applying the Michael addition to alkylidene phosphonates described in the EP patent application 0 221 611.

The esters according to the invention may also be prepared from P-C-P-structures at a lower oxidation level by oxidation



whereby in the formulas  $\text{R}^1$  to  $\text{R}^4$  and  $\text{Q}^1$  and  $\text{Q}^2$  have the meaning given above, and whereby the phosphonite structure may exist in an equilibrium with the hydrogenphosphonate structure. All conventional oxidation agents, or their solutions, such as hydrogen peroxide, perhalogen compounds, peracids, permanganate etc., come into question.

The partial esters of bisphosphonic acid according to the invention may also be prepared from other partial esters by performing an intra- or intermolecular exchange reaction.

The tetraesters II and corresponding tetraacids IV used as starting materials in the above reactions may be prepared by processes known as such from literature by constructing the P-C-P frame from its parts, for example using the above mentioned Michaelis-Becker-, Michaelis-Arbuzov- or carbanion reaction, also stepwise, whereby  $\text{R}^1$  to  $\text{R}^4$  may be chosen and advantageously introduced as parts of the bisphosphonate taking into account the structure of the desired partial ester, and by suitably substituting this frame or

an anion obtained therefrom, for example by an alkylation or an addition reaction.

5 N-substituted (aminomethylidene)bisphosphonic acid tetra-  
esters may be prepared by reacting an amino substituted  
compound with alkyl ortoformiate and reacting the imino  
ether derivative obtained as an intermediate with dialkyl  
phosphite either as such or in purified form.

10 N-substituted (aminoalkylidene)bisphosphonic acid esters  
may also be prepared for example in a reaction between  
alkenyl bisphosphonic acid esters and amino derivatives, or  
by substituting suitably (alkylidene)bisphosphonic acid  
esters.

15 O-substituted (oxyalkylidene)bisphosphonic acid tetraes-  
ters may be prepared for example by reacting suitable  
dichloroalkyl ethers with trialkyl phosphites and by  
reacting the thus obtained dialkyl (chloroalkoxymethyl)-  
20 phosphonates with sodium dialkyl phosphite.

(Thiomethylidene)bisphosphonates may suitably be prepared  
by reacting a disulfide and a methylenebisphosphonate  
anion.

25 Taking into account the preparation of a desired partial  
ester, the prepared tetraesters may, if necessary, be  
converted to other suitable tetraesters using exchange  
reactions. Thereby the groups  $OR^1$  to  $OR^4$  may be exchanged  
30 directly or over the corresponding phosphonochloride or by  
applying other known processes.

Optically active partial esters may be best prepared by  
using known optically active compounds, such as optically  
35 active alcohols, in the preparation of the above mentioned  
starting materials, intermediates and end products, or in  
the exchange reactions.

The properties of the compounds according to the invention have been tested in the following test systems.

- 5 The parathyroid hormone stimulated bone resorption inhibition activity of the compounds in vitro in mouse calvaria, as well as the inhibition of retinoid induced bone resorption in thyroparathyroidectomised rats in vivo were determined (Reynolds & Dingle (Calc Tiss Res 1970; 4:339,  
10 and Trechsel et al. (J Clin Invest 1987; 80:1679)).

Table 2: Antiresorptive activity  
Inhibition of resorption (%)

	100 $\mu$ m	150 $\mu$ mole/kg
	in vitro	in vivo
15 Clodronate	43	64
[[ (3-methyl 2-pyridinyl) amino] methylidene]bisphosphonate	51	ND
20 [[ (2-pyridinyl) amino]-methylidene]bisphosphonate	56	>100
P,P'-diethyl [[ (3-methyl 2-pyridinyl) amino]-methylidene]bisphosphonate	43	66
25 P,P'-diethyl [[ (2-pyridinyl) amino]-methylidene]bisphosphonate	33	65
monoisopropyl [[ (2-pyridinyl) thio]-methylidene]bisphosphonate	50	87

30 ND = Not determined.

From the table the superiority of the compounds of the invention, especially their better relative in vivo-antiresorptive activity is apparent when taking into account  
35 that they do not bind to hydroxy apatite, even though they inhibit crystal growth. They provide for a better therapeutic index, exhibiting lesser side effects.

The partial esters of substituted bisphosphonic acids of the formula I may be used as pharmaceuticals as such, or as their pharmacologically suitable salts, such as the alkali or ammonium salts. Such salts may be prepared by reacting the ester acids with the corresponding inorganic or organic bases. Depending on the reaction conditions, the ester salts may be formed also directly in the above mentioned reactions.

10

The new compounds I according to this invention may be administered enterally or parenterally. All conventional administration forms, such as tablets, capsules, granules, syrups, solutions, implants and suspensions come into question. Also all adjuvants for manufacture, dissolution and administration of the preparation, as well as stabilizers, viscosity regulating and dispersion agents and buffers, may be used.

20 Such adjuvants include i.a. tartrate and citrate buffers, alcohols, EDTA and other nontoxic complexing agents, solid and liquid polymers and other sterile substrates, starch, lactose, mannite, methylcellulose, talc, silicic acids, fatty acids, gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and, if desired, flavouring and sweetening agents. The dosage depends on several factors, for example on the manner of administration, species, age and individual condition. The daily doses are about 0.1 to 1000 mg, usually 1 to 100 mg per person, and they may be administered as a single dose or may be divided into several doses. In the following, examples of a typical capsule and a tablet are given:

. 30

<u>Capsule</u>	<u>mg/caps.</u>
Active ingredient	10.0 mg
Starch	20.0 mg
Magnesium stearate	1.0 mg

5

Tablet

Active ingredient	40.0 mg
Microcrystalline cellulose	20.0 mg
10 Lactose	67.0 mg
Starch	10.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

15 For medicinal use, also an intramuscularly or parenteral-  
ly administered preparation may be made, for example an in-  
fusion concentrate, wherein as adjuvants e.g. sterile  
water, phosphate buffer, NaCl, NaOH or HCl or other known  
pharmaceutical adjuvants suitable for the purpose may be  
20 used.

The compounds in ester-acid form according to the inven-  
tion are liquids or waxy substances, usually soluble in  
organic solvents and in some instances in water. The ester  
25 salts are solid, crystalline or typically powdery substan-  
ces which usually dissolve well in water, in some instances  
in organic solvents, but only certain structure types being  
poorly soluble in all solvents. The compounds are very  
stable, also in their neutral solutions at room temperatu-  
30 re.

The structure of the compounds may easily be verified with  
 $^1\text{H}$ -,  $^{13}\text{C}$ - and  $^{31}\text{P}$ -NMR-spectroscopy and FAB-massspectrometry,  
or when silylated, with EI-massspectrometry. For concentra-  
35 tion and impurity determinations  $^{31}\text{P}$ -NMR-spectroscopy is  
very suitable (85 %  $\text{H}_3\text{PO}_4$   $\delta = 0$ ). Also for polar compounds  
as such ion exchange and exclusion-HPLC may be used and for

tetraesters and silylated ester acid derivatives GLC or GC/MS may be used. From the compounds sodium and other metals were determined separately as well as the possible crystal water content. From the amine salts, nitrogen was  
5 determined.

The following examples illustrate the invention without limiting the same in any way.



Preparation of starting materialsExample A

- 5 Preparation of [[(3-methyl-2-pyridinyl)amino]methylidene]-bisphosphonic acid tetraethyl ester

A mixture of 2-amino-3-methylpyridine (0.2 moles), triethyl ortoformiate (0.24 moles) and diethylphosphite (0.42  
10 moles) was heated at 150 °C for 30 minutes, whereafter the ethanol formed in the reaction was distilled off. The mixture was cooled and the raw product was purified chromatographically (eluent methanol-dichloromethane, 1:1). Yield 37 g (49 %; 31-P NMR 18.86 ppm; CDCl<sub>3</sub>).

15

In the same manner may be prepared:

[[ (4-Methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid tetraethyl ester from 2-amino-4-methylpyridine (31-P  
20 NMR 18.60 ppm; CDCl<sub>3</sub>).

[[ (6-Methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid tetraethyl ester from 2-amino-6-methylpyridine (31-P  
NMR 18.75 ppm; CDCl<sub>3</sub>).

25

[[ (2-Pyridinyl)amino]methylidene]bisphosphonic acid tetraethyl ester from 2-aminopyridine (31-P NMR 18.62 ppm; CDCl<sub>3</sub>).

30 [[ (3-Pyridinyl)amino]methylidene]bisphosphonic acid tetraethyl ester from 3-aminopyridine.

[[ (3-Pyridinyl)amino]methylidene]bisphosphonic acid tetraisopropyl ester from 3-aminopyridine.

35

[[ (2-Pyridinyl) amino] methylidene] bisphosphonic acid tetramethyl ester from 2-aminopyridine (31-P NMR 16.00 ppm; CDCl<sub>3</sub>).

- 5 [[ (4-Pyridinyl) amino] methylidene] bisphosphonic acid tetraethyl ester from 4-aminopyridine.

[[ (3-Hydroxy-2-pyridinyl) amino] methylidene] bisphosphonic acid tetraethyl ester (31-P NMR 18.76 ppm; CDCl<sub>3</sub>).

10

[[ (4-Methoxy-3-pyridinyl) amino] methylidene] bisphosphonic acid tetraethyl ester (31-P NMR 18.15 ppm; CDCl<sub>3</sub>).

- 15 [[ (4,6-Dihydroxy-2-pyrimidyl) amino] methylidene] bisphosphonic acid tetraethyl ester.

#### Example B

- 20 Preparation of [1-hydroxy-2-(2-pyridinyl) ethylidene] bisphosphonic acid tetramethyl ester

To a chloroform solution of trimethylphosphite (0.1 moles) and dimethyl phosphite (0.1 moles) (2-pyridinyl) acetyl chloride (0.1 moles) dissolved in chloroform was slowly  
25 added at 0 °C. The mixture was heated at 80 °C for 10 hours. The solvent was evaporated at reduced pressure, and the product purified with flash chromatography (eluent methylene chloride-methanol 1:1). Yield 14 g (41 %).

- 30 In the same manner may be prepared:

[1-Hydroxy-2-(3-pyridinyl) ethylidene] bisphosphonic acid tetraisopropyl ester (31-P NMR 20.02 ppm; CDCl<sub>3</sub>).

- 35 [1-Hydroxy-2-(4-pyridinyl) ethylidene] bisphosphonic acid tetraisopropyl ester.

Example C

Preparation of [2-(2-pyridinyl)ethylidene]bisphosphonic acid tetraisopropyl ester

5 Sodium hydride (0.15 moles) was slurried in a nitrogen atmosphere into dry toluene and tetraisopropyl methylene-phosphonate (0.065 moles) was added slowly. The solution was stirred until the generation of hydrogen had ceased. 2-  
10 picolyl chloride (0.72 moles) dissolved in dimethylformamide was added slowly and the solution refluxed for 12 hours. The solvents were evaporated and the product purified with flash chromatography (eluent toluene-acetone, 1:1). Yield 58 %,

15

In the same manner may be prepared:

[[2-Pyridinyl)thio]methylidene]bisphosphonic acid tetra-  
methyl ester from 2,2'-dipyridinyl disulphide (31 P-NMR  
20 23.26 ppm; CDCl<sub>3</sub>).

[[2-Pyridinyl)thio]methylidene]bisphosphonic acid tetra-  
isopropyl ester from 2,2'-dipyridinyl disulphide (31-P NMR  
25 18.85 ppm; CDCl<sub>3</sub>).

25

[2-(3-pyridinyl)ethylidene]bisphosphonic acid tetraisopro-  
pyl ester (31-P NMR 20.13 ppm; CDCl<sub>3</sub>).

[2-(3-pyridinyl)ethylidene]bisphosphonic acid tetraethyl  
30 ester (31-P NMR 22.00 ppm; CDCl<sub>3</sub>).

[[3-Pyridinyl)thio]methylidene]bisphosphonic acid tetra-  
isopropyl ester from 3,3'-dipyridinyl disulphide.

35 [[4-Pyridinyl)thio]methylidene]bisphosphonic acid tetra-  
ethyl ester from 4,4'-dipyridinyl disulphide.

[[ (2-Pyridinyl)thio]methylidene]bisphosphonic acid tetraethyl ester from 2,2'-dipyridinyl disulphide

5 [[ (2-Pyridinyl)thio]methylidene]bisphosphonic acid isopropyl trimethyl ester from 2,2'-dipyridinyl disulphide and isopropyl trimethyl methylenebisphosphonate (31-P NMR 20.21/17.5 ppm; CDCl<sub>3</sub>).

10 [[ (4-Chlorophenyl)thio]methylidene]bisphosphonic acid tetraisopropyl ester from bis(4-chlorophenyl) disulphide (31-P NMR 18.14 ppm; CDCl<sub>3</sub>).

15 [[ (4-Chlorophenyl)thio]methylidene]bisphosphonic acid tetraethyl ester from bis(4-chlorophenyl) disulphide

[2-(2-Pyridinyl)ethylidene]bisphosphonic acid P,P'-dimethyl P',P'-diisopropyl ester from 2-picolyl chloride and P,P'-dimethyl P',P'-diisopropyl methylenebisphosphonate.

20 [2-(3-Pyridinyl)ethylidene]bisphosphonic acid P,P'-dimethyl P,P'-diisopropyl ester from 3-picolyl chloride ja P,P'-dimethyl P,P'-diisopropyl methylenebisphosphonate.

25 [2-(4-Pyridinyl)ethylidene]bisphosphonic acid tetraethyl ester from 4-picolyl chloride.

Further, by using as a base lithium diisopropylamide, one may prepare

30 [[ (4-Chlorophenyl)thio]methylidene]bisphosphonic acid P,P'-dimethyl P,P'-bis(trimethylsilyl) ester.

[2-(2-Pyridinyl)ethylidene]bisphosphonic acid P-ethyl P,P',P'-tris(trimethylsilyl) ester.

35

[2-(3-Pyridinyl)ethylidene]bisphosphonic acid P-methyl P,P',P'-tris(trimethylsilyl) ester.

[[ (4-Chlorophenyl)thio)methylidene]bisphosphonic acid P-ethyl P,P',P'-tris(trimethylsilyl) ester.

Example 1

5

Preparation of [[ (6-methyl-2-pyridinyl)amino]methylidene]-bisphosphonic acid P,P-diethyl ester

10 Into an acetonitrile solution of [[ (6-methyl-2-pyridinyl)-amino]methylidene]bisphosphonic acid tetraethyl ester (0.02 moles) and sodium iodide (0.04 moles) chlorotrimethylsilane (0.042 moles) was slowly added at room temperature. The solution was stirred for 3 hours, whereafter the solvent was evaporated at reduced pressure. The evaporation residue  
15 was dissolved in a small amount of warm water, and the solution was made alkaline with a dilute sodium hydroxide solution. The product was precipitated by adding ethanol (31-P NMR 11.34/22.79 ppm, J=34.3; D<sub>2</sub>O).

20 In a corresponding manner the following esters and their sodium salts may be prepared:

[[ (2-Pyridinyl)thio]methylidene]bisphosphonic acid P,P-diisopropyl ester from the corresponding tetraisopropyl  
25 ester (31-P NMR 9.34/20.44 ppm; J=14.9 Hz; D<sub>2</sub>O).

[[ (2-Pyridinyl)thio]methylidene]bisphosphonic acid P,P-diethyl ester from the corresponding tetraethyl ester.

30 [[ (3-Pyridinyl)thio]methylidene]bisphosphonic acid P,P-diisopropyl ester from the corresponding tetraisopropyl ester.

35 [[ (4-Pyridinyl)thio]methylidene]bisphosphonic acid P,P-diethyl ester from the corresponding tetraethyl ester.

[2-(2-Pyridinyl)ethylidene]bisphosphonic acid P',P'-diisopropyl ester from the corresponding P,P-dimethyl P',P'-diisopropyl ester.

5 [2-(3-Pyridinyl)-1-hydroxyethylidene]bisphosphonic acid P',P'-diethyl ester from the corresponding P,P-dimethyl P',P'-diethyl ester.

10 [[(4-Chlorophenyl)thio]methylidene]bisphosphonic acid P,P-diisopropyl ester from the corresponding tetraisopropyl ester (31-P NMR 10.84/21.38 ppm, J=15.2 Hz; D<sub>2</sub>O).

15 [[(6-Methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid P,P-diethyl ester from the corresponding tetraethyl ester (31-P NMR 11.34/22.79 ppm, J=34.3 Hz; D<sub>2</sub>O).

20 [[(4-Methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid P,P-diethyl ester from the corresponding tetraethyl ester (31-P NMR 11.43/22.83 ppm, J=35.0 Hz; D<sub>2</sub>O).

[2-(3-Pyridinyl)ethylidene]bisphosphonic acid P,P-diethyl ester from the corresponding tetraethyl ester.

25 (3-Pyridinylamino)methylidene]bisphosphonic acid P,P-diethyl ester from the corresponding tetraethyl ester.

### Example 2

30 Preparation of [[(4-chlorophenyl)thio]methylidene]-bisphosphonic acid monoisopropyl ester and its trisodium salt

35 The tetraisopropyl ester of [[(4-chlorophenyl)thio]methylidene]bisphosphonic acid (0.02 moles) was dissolved in dichloromethane, and to the solution was slowly added at room temperature bromotrimethylsilane (0.062 moles). The solution was stirred at room temperature for 3 hours, whereafter the solvent was evaporated at reduced pressure.

The evaporation residue was dissolved in a small amount of water and the solution was made alkaline with a dilute sodium hydroxide solution. The product was precipitated by adding ethanol (31-P NMR 12.21/18.25 ppm,  $J=9.8$  Hz;  $D_2O$ ).

5

Example 3

Preparation of [[(2-pyridyl)thio]methylidene]bisphosphonic acid triisopropyl ester and its sodium salt

10

[[ (2-Pyridyl)thio]methylidene]bisphosphonic acid tetraiso-propyl ester (0.02 moles) was dissolved in acetonitrile, and to the solution chloro(tert-butyl)(dimethyl)silane (0.022 moles) dissolved in acetonitrile was slowly added.

15

The solution was stirred for 4 hours at 60 °C. The solvent was evaporated and the evaporation residue was dissolved in a small amount of water. The solution was made alkaline with a dilute sodium hydroxide solution and the product precipitated by adding ethanol (31-P NMR 7.78/23.76 ppm,  $J=9.6$  Hz;  $D_2O$ ).

20

In a corresponding manner the following compounds using in the place of chloro(tert-butyl)(dimethyl)silane for example bromotrimethylsilane (1 equivalent) may be prepared:

25

[2-(2-Pyridinyl)ethylidene]bisphosphonic acid trimethyl ester from the corresponding tetramethyl ester.

30

[2-(3-Pyridinyl)ethylidene]bisphosphonic acid triethyl ester from the corresponding tetraethyl ester.

[[ (3-Pyridinyl)thio]methylidene]bisphosphonic acid triethyl ester from the corresponding tetraethyl ester.

35

[[ (2-Pyridinyl)thio]methylidene]bisphosphonic acid dimethyl isopropyl ester from the corresponding isopropyl trimethyl ester.

[2-(3-pyridinyl)ethylidene]bisphosphonic acid triisopropyl ester (31-P NMR 26.23/15.09 ppm;  $\text{CDCl}_3$ ).

- 5    [[(4-Methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid triethyl ester from the corresponding tetraethyl ester (31-P NMR 8.62/26.15 ppm,  $J=25.4$  Hz;  $\text{D}_2\text{O}$ ).

- 10    [1-Hydroxy-2-(3-pyridinyl)ethylidene]bisphosphonic acid triisopropyl ester from the corresponding tetraisopropyl ester.

Example 4

- 15    Preparation of [[(3-methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester

- 20    [[(3-methyl-2-pyrdinyl)amino]methylidene] bisphosphonic acid tetraethyl ester (0.015 moles) was dissolved in aqueous ethanol and concentrated sodium hydroxide solution (0.05 moles) was added to the solution. The solution was stirred over night. The solvent was evaporated and the evaporation residue stirred into ethanol. The product was filtered and dried (31-P NMR 16.60 ppm;  $\text{D}_2\text{O}$ ).

- 25    In a corresponding manner may be prepared:

[[ (2-Pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester (31-P NMR 16.37 ppm;  $\text{D}_2\text{O}$ ).

- 30    [[(4-Pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester.

- 35    [[(4-chlorophenyl)thio]methylidene]bisphosphonic acid P,P'-diisopropyl ester from the corresponding tetraisopropyl ester (31-P NMR 14.00 ppm;  $\text{D}_2\text{O}$ ).



[2-(2-Pyridinyl)ethylidene]bisphosphonic acid P,P'-diisopropyl ester from the corresponding tetraisopropyl ester.

5 [2-(3-Pyridinyl)ethylidene]bisphosphonic acid P,P'-diethyl ester from the corresponding tetraethyl ester.

10 [1-Hydroxy-2-(2-pyridinyl)ethylidene]bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester.

[1-Hydroxy-2-(3-pyridinyl)ethylidene]bisphosphonic acid P,P'-diethyl ester from the corresponding tetraethyl ester.

15 [[(2-Hydroxy-3-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester from the corresponding tetraethyl ester.

20 [[(2-Methoxy-3-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester from the corresponding tetraethyl ester.

25 [[(4,6-Dihydroxy-2-pyrimidyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester from the corresponding tetraethyl ester.

#### Example 5

30 Preparation of [[(6-methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester and its disodium salt

35 The tetraethyl ester of [[(6-methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid (0.009 moles) was dissolved in a mixture of morpholine (40 ml) and dichloromethane (50 ml). The solution was stirred for a day. The solvent was evaporated and the morpholinium salt of the product was dissolved in acetone. To the solution a sodium hydroxide

solution was added (0.02 moles), whereby the product precipitated in the form of the disodium salt ( $^{31}\text{P}$  NMR 16.45 ppm;  $\text{D}_2\text{O}$ ).

- 5 In the same manner may be prepared, also using instead of morpholine e.g. piperidine, 2-methylpiperidine or 4-benzylpiperazine
- [[ (4-pyridinyl) amino] methylidene] bisphosphonic acid P,P'-dimethyl ester,
- 10 [[ (3-pyridinyl) thio] methylidene] bisphosphonic acid P,P'-diethyl ester,
- [[ (3-pyridinyl) amino] methylidene] bisphosphonic acid P,P'-dimethyl ester,
- [2-(2-pyridinyl) ethylidene] bisphosphonic acid P,P'-dimethyl
- 15 ester.

#### Example 6

- Preparation of [[ (4-methyl-2-pyridinyl) amino] methylidene)-
- 20 bisphosphonic acid P,P'-diethyl ester and its disodium salt

The tetraethyl ester of [[ (4-methyl-2-pyridinyl) amino] methylidene) bisphosphonic acid (0.02 moles) was dissolved in dichloromethane and to the solution bromotrimethylsilane (0.042 moles) was slowly added at room temperature.

25 The solution was stirred for 3 hours. The solvent was evaporated at reduced pressure. To the evaporation residue, a sodium hydroxide solution (0.04 moles) was added as well as an equal volume of ethanol, whereby the product precipitated as the disodium salt ( $^{31}\text{P}$  NMR 16.39 ppm;  $\text{D}_2\text{O}$ ).

30

In a corresponding manner may be prepared:

- [2-(2-Pyridinyl) ethylidene] bisphosphonic acid P,P'-diisopropyl ester from the corresponding tetraisopropyl ester.
- 35

[[ (4-Chlorophenyl)thio]methylidene)bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester.

5 [[ (2-Pyridinyl)thio]methylidene]bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester.

[2-(2-Pyridinyl)ethylidene]bisphosphonic acid P,P'-diisopropyl ester from the corresponding P,P'-dimethyl P,P'-diisopropyl ester.

10

[[ (3-Pyridinyl)thio]methylidene]bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester.

15 [2-(3-Pyridinyl)ethylidene]bisphosphonic acid P,P'-diisopropyl ester from the corresponding P,P'-dimethyl P,P'-diisopropyl ester.

20 [1-Hydroxy-2-(3-pyridinyl)ethylidene]bisphosphonic acid P,P'-diisopropyl ester from the corresponding tetraisopropyl ester.

#### Example 7

25 Preparation of [[ (6-methyl-2-pyridinyl)amino]methylidene)bisphosphonic acid monoethyl ester and its trisodium salt

30 [[ (6-methyl-2-pyridinyl)amino]methylidene)bisphosphonic acid P,P'-diethyl ester prepared according to the Example 4 (0.01 moles) was slurried in a 15% hydrochloric acid solution and the solution was stirred at 80 °C. The progress of the reaction was followed with <sup>31</sup>P NMR. After the reaction had ceased the mixture was evaporated to dryness, the evaporation residue dissolved in a sodium hydroxide solution and the trisodium salt formed precipitated by  
35 adding ethanol. The product was filtered and dried (yield 60 %, <sup>31</sup>P NMR 11.73/19.11 ppm; J=24.7 Hz; D<sub>2</sub>O).

In a corresponding manner may be prepared:

5 [1-Hydroxy-2-(2-pyridinyl)ethylidene]bisphosphonic acid  
monoisopropyl ester from the corresponding P,P'-diisopropyl  
ester.

10 [2-(3-pyridinyl)ethylidene]bisphosphonic acid monoisopropyl  
ester (31-P NMR 18.76/17.45 ppm; CDCl<sub>3</sub>).

[[2-Pyridinyl)thio]methylidene]bisphosphonic acid mo-  
noisopropyl ester from the corresponding P,P'-diisopropyl  
ester (31-P NMR 11.79/18.05 ppm, J=9.6 Hz; D<sub>2</sub>O).

15 [1-Hydroxy-2-(3-pyridinyl)ethylidene]bisphosphonic acid  
monoisopropyl ester from the corresponding P,P'-diisopropyl  
ester.

20 [[(3-Pyridinyl)thio]methylidene]bisphosphonic acid mo-  
noisopropyl ester from the corresponding P,P'-diisopropyl  
ester (31-P NMR 11.79/18.05 ppm, J=9.6 Hz; D<sub>2</sub>O).

25 [[(4-Methyl-2-pyridinyl)amino]methylidene]bisphosphonic  
acid monomethyl ester.

[[3-Methyl-2-pyridinyl)amino]methylidene]bisphosphonic  
acid monomethyl ester.

30 [2-(2-Pyridinyl)ethylidene]bisphosphonic acid monoisopropyl  
ester.

Example 8

Preparation of [[(2-pyridyl)thio]methylidene]bisphosphonic acid P,P'-diisopropyl ester

5 [[(2-pyridyl)thio]methylidene]bisphosphonic acid tetraisopropyl ester (0.01 moles) was dissolved in acetone, and to the solution sodium iodide (0.023 moles) was added. The solution was stirred at room temperature for 8 hours, 10 whereafter it was filtered. The solvent was evaporated. The product was isolated from the evaporation residue as the disodium salt in a manner described in the previous examples (yield 59%, <sup>31</sup>-P NMR 14.09 ppm; D<sub>2</sub>O).

15 In the corresponding manner may be prepared:

[[2-(3-Pyridinyl)thio]methylidene]bisphosphonic acid P,P'-dimethyl ester from the corresponding tetramethyl ester (31-P NMR).

20 [[2-(3-Pyridinyl)thio]methylidene]bisphosphonic acid P,P'-diisopropyl ester from the corresponding tetraisopropyl ester.

25 [1-Hydroxy-2-(3-pyridinyl)ethylidene]bisphosphonic acid P,P'-diethyl ester from the corresponding tetraethyl ester.

30 [[2-(4-Pyridinyl)thio]methylidene]bisphosphonic acid P,P'-diisopropyl ester from the corresponding tetraisopropyl ester.

[1-Hydroxy-2-(2-pyridinyl)ethylidene]bisphosphonic acid P,P'-diethyl ester from the corresponding tetraethyl ester.

Example 9

Preparation of [1-hydroxy-2-(3-pyridinyl)ethylidene]bisphosphonic acid monomethyl ester

- 5 Finely ground [1-hydroxy-2-(3-pyridinyl)ethylidene]bisphosphonic acid (0.005 moles) was slurried into 100 ml of chloroform and to the mixture 25 ml of an appr. 2% ether solution of diazomethane was added at room temperature.
- 10 After the addition, mixing was continued for 1 hour. The mixture was evaporated under reduced pressure (yield 38 %).

Example 10

- 15 Preparation of [[(2-pyridinyl)thio]methylidene]bisphosphonic acid monoisopropyl ester and its trisodium salt

- [[ (2-pyridinyl)thio]methylidene]bisphosphonic acid tetraisopropyl ester (0.01 moles) was dissolved in toluene and
- 20 to the solution methane sulphonic acid (0.06 moles) was added. The solution was stirred while heating and the progress of hydrolysis was followed with  $^{31}\text{P}$  NMR. The mixture was cooled and the solvent evaporated under reduced pressure. The evaporation residue was dissolved in a dilute
- 25 sodium hydroxide solution and the product was precipitated by adding acetone (yield 62 %,  $^{31}\text{P}$  NMR 11.79/18.05 ppm,  $J = 9.6 \text{ Hz}$ ;  $\text{D}_2\text{O}$ ).

In the same manner may be prepared:

- 30 [2-(3-Pyridinyl)-1-hydroxyethylidene]bisphosphonic acid P,P'-diisopropyl ester from the corresponding tetraisopropyl ester.

- 35 [2-(3-Pyridinyl)-1-hydroxyethylidene]bisphosphonic acid monomethyl ester from the corresponding tetramethyl ester.

[2-(2-Pyridinyl)-1-hydroxyethylidene]bisphosphonic acid P,P'-diisopropyl ester from the corresponding tetraisopropyl ester.

- 5 [2-(3-Pyridinyl)ethylidene]bisphosphonic acid P,P-diisopropyl ester from the corresponding tetraisopropyl ester.

Example 11

- 10 Preparation of [[(4-chlorophenyl)thio]methylidene]-bisphosphonic acid P,P'-dimethyl ester and its disodium salt

- A mixture of [[(4-chlorophenyl)thio]methylidene]-  
15 bisphosphonic acid P,P'-dimethyl P,P'-bis(trimethylsilyl) ester (0.01 moles) and dilute hydrochloric acid was stirred at 0 °C for 0.5 hours. To the filtered solution dilute sodium hydroxide was added (0.01 moles excess) and the product precipitated with ethanol.

20

In a corresponding manner may be prepared

[2-(2-Pyridinyl)ethylidene]bisphosphonic acid monoethyl ester

- 25 [2-(3-Pyridinyl)ethylidene]bisphosphonic acid monomethyl ester

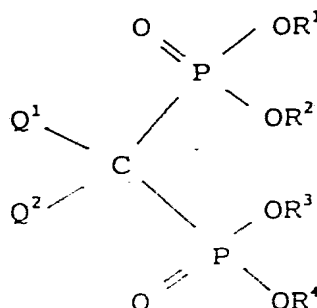
[[ (4-chlorophenyl)thio]methylidene]bisphosphonic acid monoethyl ester.

## Claims

1. Novel bisphosphonic acid derivatives having the formula I

5

10



I

15

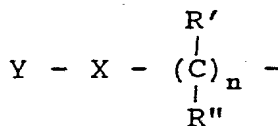
in which formula

$R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  independently are a straight or branched, optionally unsaturated  $C_1$ - $C_{10}$ -alkyl, optionally unsaturated  $C_3$ - $C_{10}$ -cycloalkyl, aryl, aralkyl, silyl  $\text{SiR}_3$  or hydrogen, whereby in the formula I at least one of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  is hydrogen and at least one of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  is different from hydrogen,

$Q^1$  is hydrogen, hydroxyl, halogen, amino  $\text{NH}_2$ , or  $\text{OR}'_1$ , wherein  $R'_1$  is  $C_1$ - $C_4$ -alkyl or acyl,

25

$Q^2$  is the group



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wherein Y is an optionally substituted, saturated, partly saturated or aromatic six-membered heterocyclic group, or a carbocyclic aromatic group, whereby the heterocyclic groups can contain 1 to 3 heteroatoms from the group N, O and S, X is a bond, O, S or  $\text{NR}''$ , wherein  $R''$  is hydrogen

35



or lower alkyl with 1 to 4 C-atoms, acyl, n is the integer 0 to 6,  
and R' and R'' are hydrogen or lower alkyl with 1 to 4 C-atoms, provided that as a ring atom of the ring Y and/or a  
5 chain atom of the group X, there is always at least one heteroatom from the group of O, N and S,  
including the stereoisomers, such as the geometrical isomers and the optically active isomers, of the compounds, as well as the pharmacologically acceptable salts of the com-  
10 pounds.

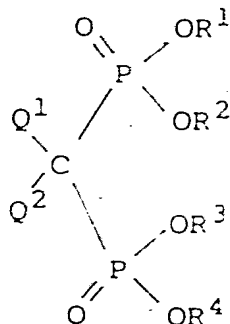
2. Mono- or dimethyl, mono- or diethyl, mono- or diisopropyl esters of the formula I according to the Claim 1, wherein Q<sup>1</sup> is hydrogen and Y is unsubstituted or methyl-  
15 substituted pyridine or piperidine, n is 0 and X is NH, or S.

3. Compound of the formula I according to the Claim 1, which is  
20 [[(6-methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester,  
[[ (2-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester,  
[[ (2-pyridinyl)amino]methylidene]bisphosphonic acid P,P-  
25 methyl ester,  
[[ (3-methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester,  
[[ (4-methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-diethyl ester,  
30 [[ (2-pyridinyl)thio]methylidene]bisphosphonic acid monoisopropyl ester,  
[[ (4-chlorophenyl)thio]methylidene]bisphosphonic acid P,P'-dimethyl and monoethyl ester,  
[[ (6-methyl-2-pyridinyl)amino]methylidene]bisphosphonic  
35 acid monoethyl ester,  
[[ (3-methyl-2-pyridinyl)amino]methylidene]bisphosphonic acid monomethyl ester,

- [[1-hydroxy-2-(3-pyridinyl)]ethylidene]bisphosphonic acid  
 monoisopropyl ester,  
 [[1-hydroxy-2-(3-pyridinyl)]ethylidene]bisphosphonic acid  
 monomethyl ester,  
 5 [2-(2-pyridinyl)ethylidene]bisphosphonic acid monoisopropyl  
 ester,  
 [2-(3-pyridinyl)ethylidene]bisphosphonic acid monomethyl  
 ester,  
 [[(3-pyridinyl)amino]methylidene]bisphosphonic acid P,P'-  
 10 dimethyl ester,  
 [[(3-pyridinyl)thio]methylidene]bisphosphonic acid P,P'-  
 diethyl ester,  
 [[(4-pyridinyl)thio]methylidene]bisphosphonic acid P,P'-  
 diethyl ester,  
 15 [[(3-pyridinyl)thio]methylidene]bisphosphonic acid mo-  
 noisopropyl ester.

4. Process for the preparation of the compounds according  
 to the Claim 1, **characterized** in that

a) a methylenebisphosphonic acid tetraester of the formu-  
 la II



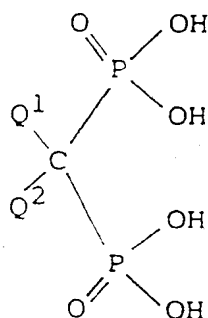
in which formula  $\text{Q}^1$  and  $\text{Q}^2$  have the same meaning as in the  
 35 Claim 1, and  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  have the same meaning as in  
 the Claim 1, except hydrogen, is selectively hydrolysed

- to a triester corresponding to the formula I, wherein one of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  has the meaning of hydrogen, or a salt thereof, or

- to a diester corresponding to the formula I, wherein two of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  have the meaning of hydrogen, or a salt thereof, or

- to a monoester corresponding to the formula I, wherein three of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  have the meaning of hydrogen, or a salt thereof, or

b) a bisphosphonic acid of the formula



VII

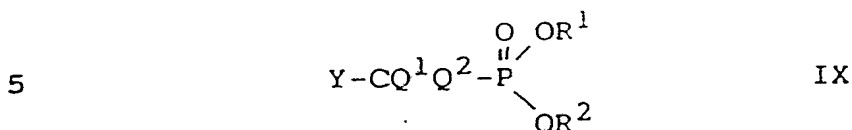
or a metal or ammonium salt of this compound, or the corresponding acid tetrachloride, wherein  $Q^1$  and  $Q^2$  have the same meaning as in the Claim 1, is esterified selectively by reacting the same with an esterification reagent corresponding to the desired groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$ ,

- to a monoester corresponding to the formula I, wherein three of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  have the meaning of hydrogen, or

- to a diester corresponding to the formula I, wherein two of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  have the meaning of hydrogen, or

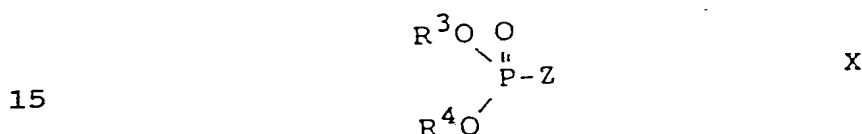
- to a triester corresponding to the formula I, wherein one of the groups  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  has the meaning of hydrogen, or to the corresponding ester salts of the said partial esters, or

c) a phosphonate having the formula



is reacted with an activated phosphate or a hydrogen phosphonate corresponding to the formula X

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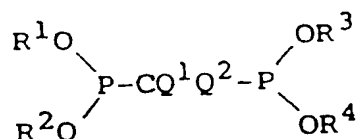
wherein in the formulas Y is hydrogen, hydroxy or halogen or other leaving group, Z is hydrogen, halogen, acyloxy, sulphonyloxy, alkoxy or aryloxy, and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> and Q<sup>1</sup> and Q<sup>2</sup> have the same meaning as in the formula I, or Q<sup>1</sup> and Q<sup>2</sup> form a double-bonded oxygen or an imino group, or is reacted with a phosphite corresponding to the formula X, or

25

d) a bisphosphonate corresponding to the formula I, which instead of Q<sup>2</sup> has a carbanion site, is reacted with ω-leaving group substituted Q<sup>2</sup>, or a bisphosphonate corresponding to the formula I, which instead of Q<sup>2</sup> contains a leaving group, is reacted with a ω-carbanion corresponding to Q<sup>2</sup>, or a (Q<sup>2</sup>-C<sub>1</sub>)-ω-carbanion is added by Michael addition in alkylidenebisphosphonates, or

e) a bisphosphonite compound having the formula

35



5

wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  and  $\text{Q}^1$  and  $\text{Q}^2$  have the same meaning as in the formula I, or the corresponding hydrogen phosphonate compound, is oxidized to a compound of the formula I, and

10




if desired, the partial ester acids obtained according to steps a) to e) are converted to partial ester salts, or the partial ester salts obtained are converted to the partial ester acids, and/or, if desired, a compound obtained according to the formula I is converted into some other compound according to the formula I by hydrolyzing, esterification or transesterification, and/or in a compound of the formula I, a group  $\text{Q}^1$  is converted into another group  $\text{Q}^1$  within the scope of the definition.

15  
20

5. Pharmaceutical composition, **characterized** in that it contains as the active agent a compound having the formula I according to Claim 1.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/FI 91/00395

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC <b>IPC5: C 07 F 9/58, 9/40, A 61 K 31/66</b>																	
<b>II. FIELDS SEARCHED</b> <div style="text-align: right; margin-right: 100px;">Minimum Documentation Searched<sup>7</sup></div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%;">Classification System</th> <th style="width: 80%;">Classification Symbols</th> </tr> <tr> <td style="height: 40px; vertical-align: bottom;">IPC5</td> <td style="vertical-align: bottom;">C 07 F</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched<sup>8</sup></div>			Classification System	Classification Symbols	IPC5	C 07 F											
Classification System	Classification Symbols																
IPC5	C 07 F																
<b>SE,DK,FI,NO classes as above</b>																	
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%;">Category *</th> <th style="width: 60%;">Citation of Document,<sup>11</sup> with indication, where appropriate, of the relevant passages<sup>12</sup></th> <th style="width: 30%;">Relevant to Claim No.<sup>13</sup></th> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td>US, A, 3962318 (AL F. KERST) 8 June 1976, see compound 41 --</td> <td style="text-align: center; vertical-align: top;">1</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>WO, A1, 8703598 (LEO PHARMACEUTICAL PRODUCTS LTD. A/S (LÖVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB)) 18 June 1987, see especially examples 14 and 15 --</td> <td style="text-align: center; vertical-align: top;">1-5</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A2, 0186405 (THE PROCTER &amp; GAMBLE COMPANY) 2 July 1986, see pages 5-10, 19-28 --</td> <td style="text-align: center; vertical-align: top;">1-5</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>Chemical Abstracts, Vol. 111, No. 19, 6 November 1989, (Columbus, Ohio, US), see page 748, abstract 174388h, &amp; JP, A, 63295595, (YAMANOCHI PHARMACEUTICAL CO., LTD.) 1 December 1988 see reg.no. 121167-73-5 --</td> <td style="text-align: center; vertical-align: top;">1-5</td> </tr> </table>			Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	X	US, A, 3962318 (AL F. KERST) 8 June 1976, see compound 41 --	1	A	WO, A1, 8703598 (LEO PHARMACEUTICAL PRODUCTS LTD. A/S (LÖVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB)) 18 June 1987, see especially examples 14 and 15 --	1-5	A	EP, A2, 0186405 (THE PROCTER & GAMBLE COMPANY) 2 July 1986, see pages 5-10, 19-28 --	1-5	A	Chemical Abstracts, Vol. 111, No. 19, 6 November 1989, (Columbus, Ohio, US), see page 748, abstract 174388h, & JP, A, 63295595, (YAMANOCHI PHARMACEUTICAL CO., LTD.) 1 December 1988 see reg.no. 121167-73-5 --	1-5
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents:<sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>																	
<b>IV. CERTIFICATION</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;">           Date of the Actual Completion of the International Search   <b>12th March 1992</b> </td> <td style="width: 50%; padding: 5px;">           Date of Mailing of this International Search Report   <b>1992 -03- 2 0</b> </td> </tr> <tr> <td style="width: 50%; padding: 5px;">           International Searching Authority   <div style="text-align: center;"><b>SWEDISH PATENT OFFICE</b></div> </td> <td style="width: 50%; padding: 5px;">           Signature of Authorized Officer   <div style="text-align: center;">   <b>Göran Karlsson</b> </div> </td> </tr> </table>			Date of the Actual Completion of the International Search  <b>12th March 1992</b>	Date of Mailing of this International Search Report  <b>1992 -03- 2 0</b>	International Searching Authority  <div style="text-align: center;"><b>SWEDISH PATENT OFFICE</b></div>	Signature of Authorized Officer  <div style="text-align: center;">   <b>Göran Karlsson</b> </div>											
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International Searching Authority  <div style="text-align: center;"><b>SWEDISH PATENT OFFICE</b></div>	Signature of Authorized Officer  <div style="text-align: center;">   <b>Göran Karlsson</b> </div>																

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	EP, A1, 0282320 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 14 September 1988, see especially example 13 -- -----	1-5

## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE<sup>1</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers....., because they relate to subject matter not required to be searched by this Authority, namely:

1 and 5

2. ☒ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The scope of claim 1 and 5 is so broadly formulated that a very wide range of structures is included. These claims have thus not been fully searched.

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING<sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO. PCT/FI 91/00395**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 01/02/92. The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3962318	76-06-08	BE-A- 765633	71-10-13
		CA-A- 986944	76-04-06
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		LU-A- 62974	72-02-23
		NL-A- 7104745	71-10-15
		US-A- 3705191	72-12-05
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		US-A- 3833690	74-09-03
		US-A- 3846482	74-11-05
		US-A- 3846483	74-11-05
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		AU-D- 5153485	86-06-26
		JP-A- 61210033	86-09-18
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		AU-D- 1289788	88-09-08
		JP-A- 2000185	90-01-05
		US-A- 4973576	90-11-27